



Assosiasjoner mellom muskelmål, overlevelse og toksisitet av cytostatika ved avansert ikke-småcellet lungekreft

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Pasienter med avansert kreft

- mange eldre
- komorbiditet er vanlig
- mange med redusert Performance status
- ufrivillig vekttap

Phase III Study by the Norwegian Lung Cancer Study Group: Pemetrexed Plus Carboplatin Compared With Gemcitabine Plus Carboplatin As First-Line Chemotherapy in Advanced Non-Small-Cell Lung Cancer

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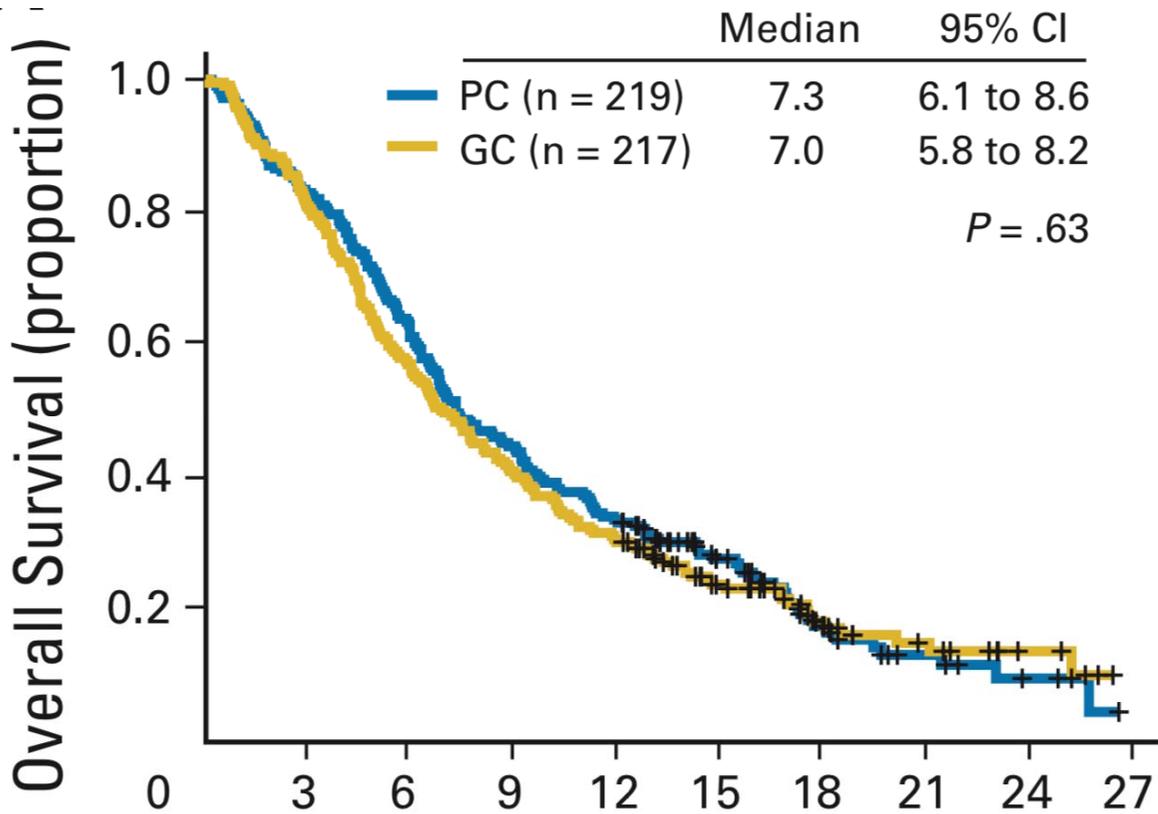


Table 4. Nonhematologic Grade 3 or 4 Adverse Events During the Study Treatment Period

Grade 3 or 4 Adverse Event	Pemetrexed/Carboplatin (n = 219)		Gemcitabine/Carboplatin (n = 217)		P
	No. of Patients	%	No. of Patients	%	
Neutropenic infection	17	8	18	9	.85
Infections without neutropenia	19	9	19	9	.98
Nausea	6	3	9	4	.43
Thrombocytopenic bleedings	5	2	9	4	.27
Deep venous thrombosis	0	0	3	1	.12
Lung embolism	0	0	4	2	.06
Acute myocardial infarction	1	1	2	1	.62
Mucositis	2	1	0	0	.50
Other	4	2	12	6	.04

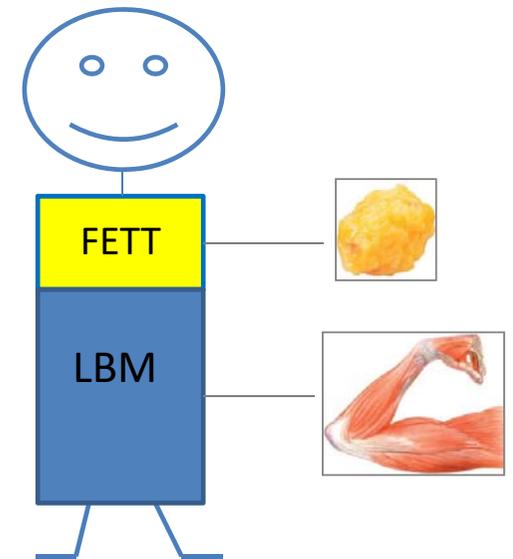
Fordeling av legemidler

- Individuell tilpasning av dosering med cellegift; estimering av kroppsoverflate (BSA, m²) beregnet ut fra pasientens høyde og vekt
- De fleste cellegiftstoffer er vannløselige
- Distribusjonsvolum avhengig av den relative mengden fett og fettfri-masse

Kroppssammensetning

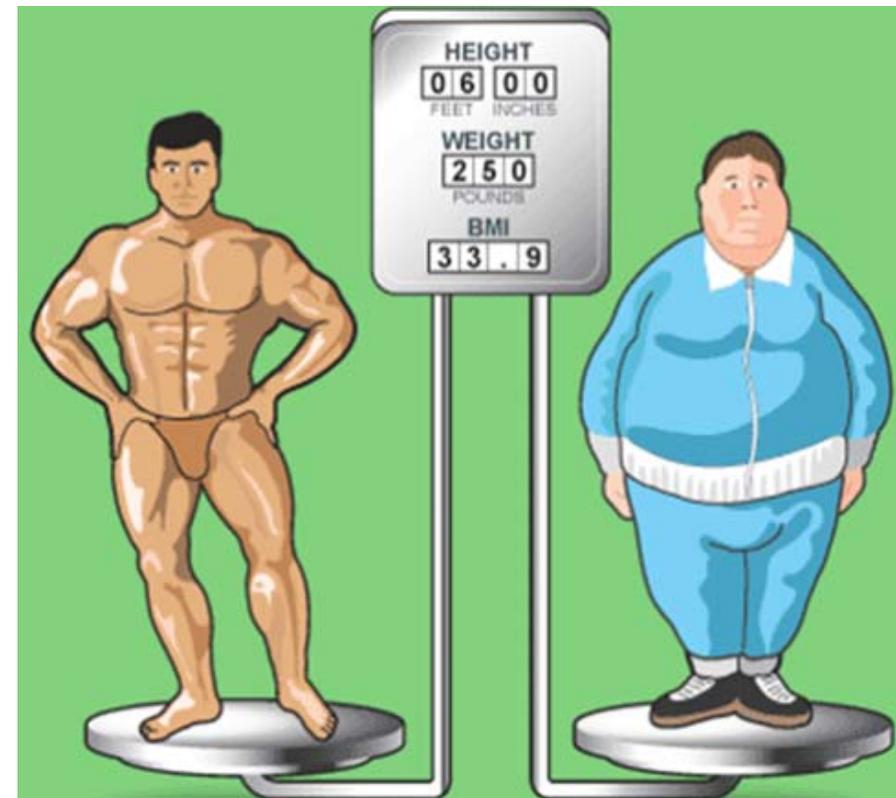
Menneskekroppen kan deles inn i to hoveddeler

- fettmasse
- fettfri-masse (lean body mass (LBM)) der skjelettmuskulatur utgjør den største andelen



Bakgrunn, kroppssammensetning

- Påvirkes av bl.a alder, kjønn, fysisk aktivitet, kosthold og sykdom
- Store individuelle forskjeller
- Den relative andel av fettvev og muskelvev vises ikke på utsiden og fremgår ikke av høyde og vekt



Bakgrunn, kroppssammensetning

- Lav muskelmasse (kalles ofte sarcopeni) er ikke forbeholdt pasienter med lav kroppsvekt eller cachexia, men ses også hos normalvektige og overvektige
- Det er vist at lav muskelmasse hos kreftpasienter kan knyttes opp mot lavere funksjonsnivå og redusert overlevelse

Rolland et al, Am J Clin Nutr 2009

Prado et al, Lancet Oncol 2008

Prado et al, Clin Cancer Res 2009

Bakgrunn, kroppssammensetning

- Noen mindre studier viste at pasienter med lav muskelmasse hadde økt toksisitet av cellegiftbehandling
 - tykktarmskreft (5-FU-basert cellegift)
 - brystkreft (capecitabine, epirubicin)
 - nyrekreft (sorafenib)

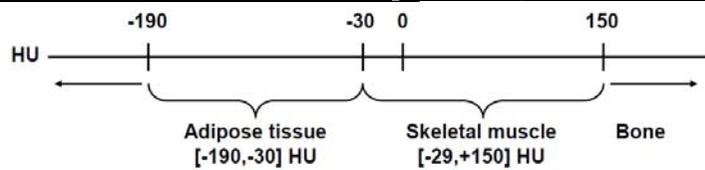
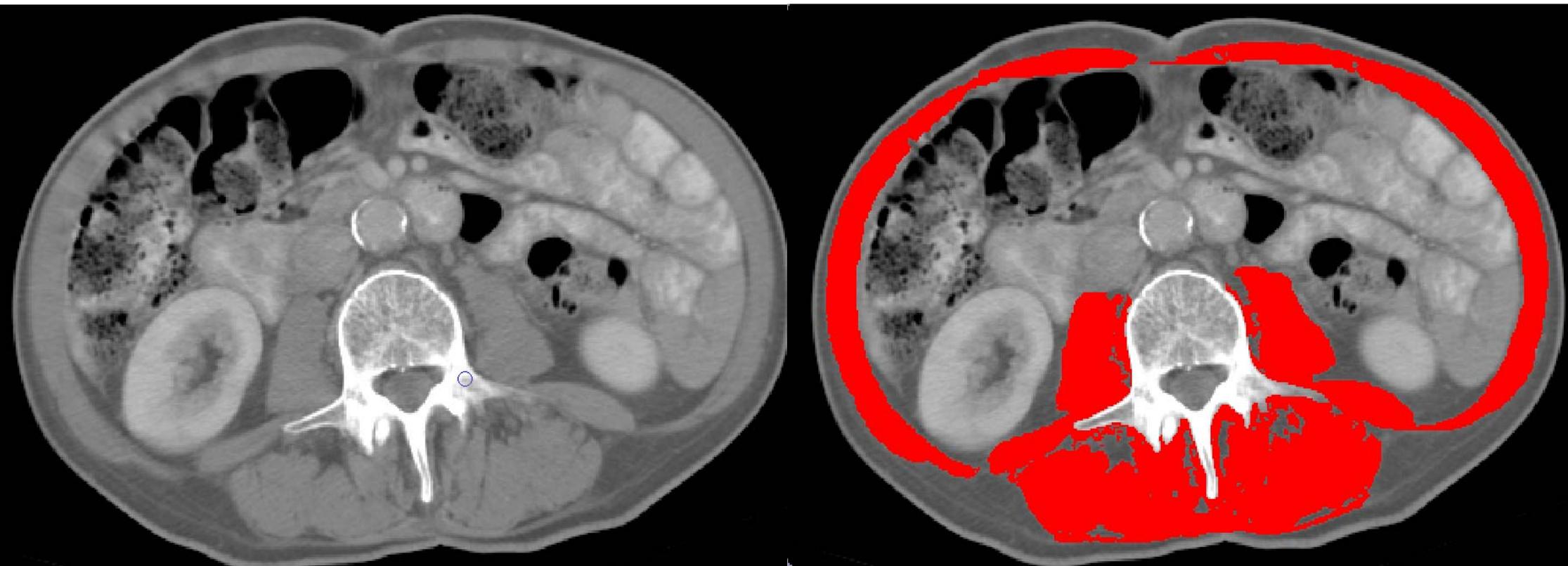
Prado et al. Clin Cancer Res 2007

Prado et al. Clin Cancer Res 2009

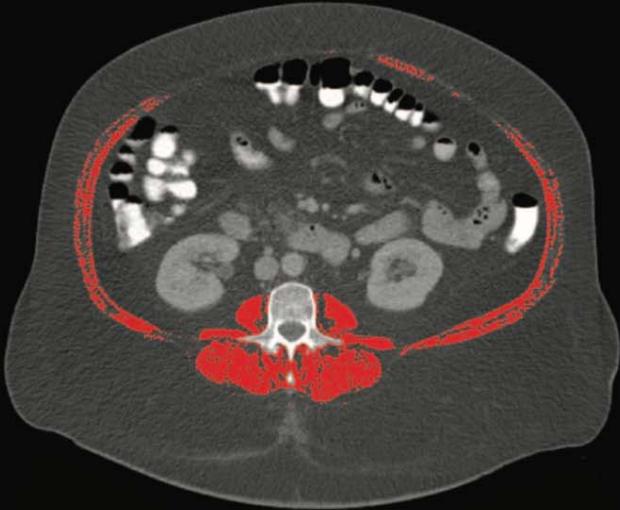
Prado et al. Cancer Chemother Pharmacol 2011

Antoun et al. Ann Oncol 2010

Måling av kroppssammensetning



B₁



BMI, 40.2 kg/m²

B₂



BMI, 28.1 kg/m²

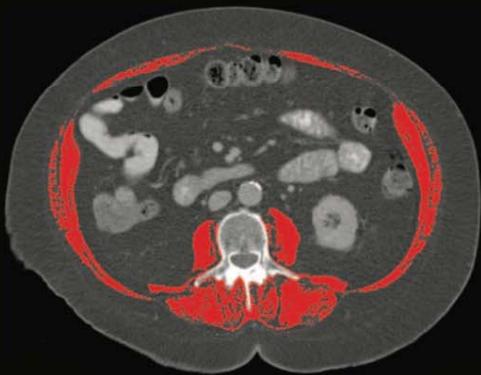
B₃



BMI, 15.3 kg/m²

Identical SMI,
29.7 cm²/m²

B₄



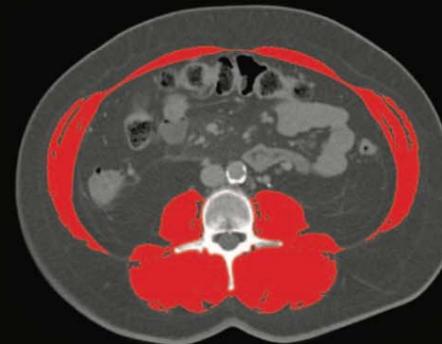
SMI, 33.7 cm²/m²

B₅



SMI, 46.3 cm²/m²

B₆



SMI, 58.3 cm²/m²

Identical BMI,
29.4 kg/m²

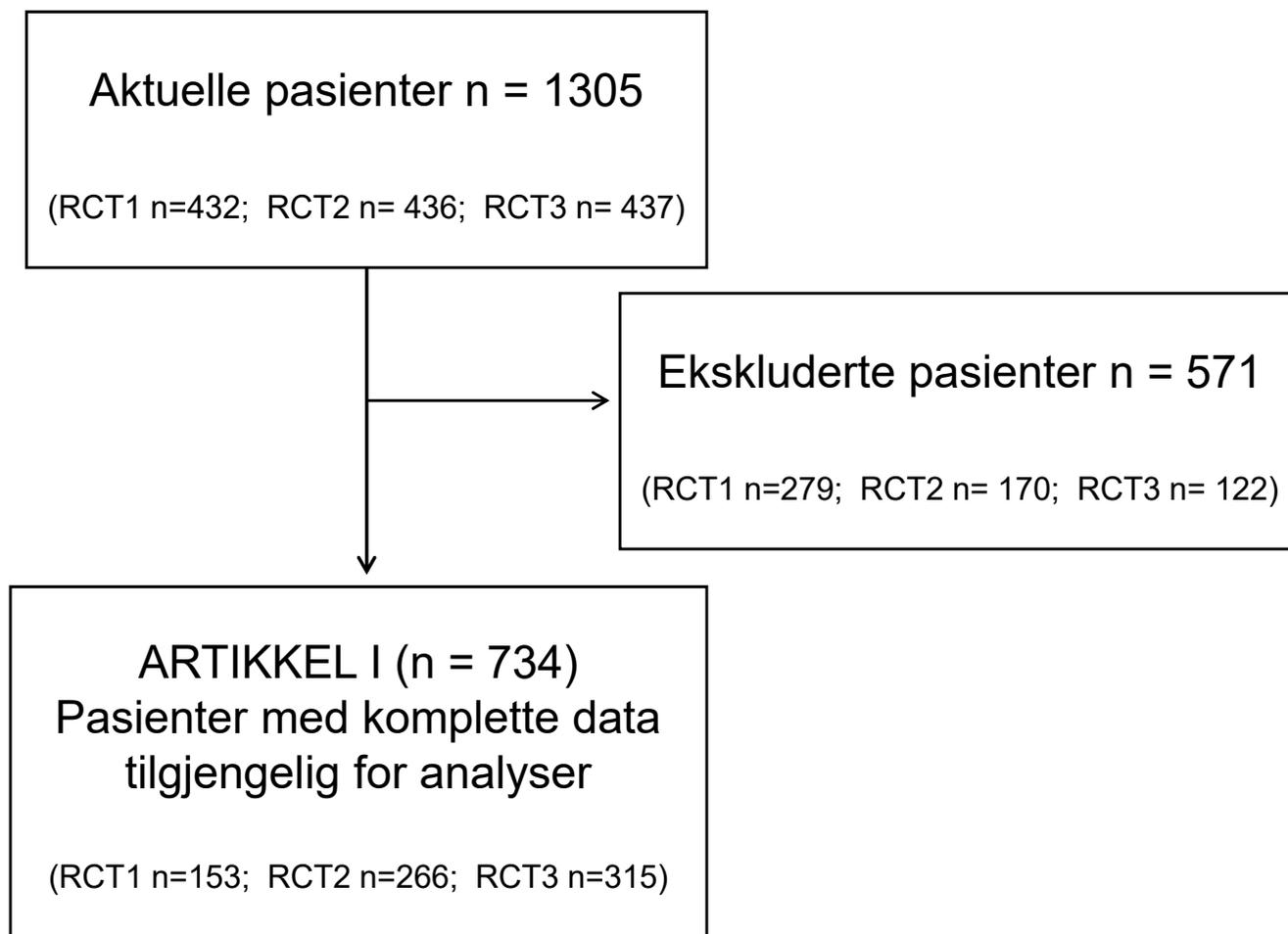


Original article

Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer



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	Univariable analyses		SMI Multivariable analyses		SMD Multivariable analyses	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
SMI (cm ² /m ²)	1.00 (0.99–1.01)	0.333	0.99 (0.98–1.01)	0.329	–	–
SMI (cm ² /m ²), males only	0.98 (0.97–1.00)	0.015	–	–	–	–
SMI (cm ² /m ²), females only	0.99 (0.97–1.01)	0.373	–	–	–	–
SMD	0.99 (0.98–1.00)	0.057	–	–	0.98 (0.97–0.99)	0.001
Adjusting factors						
Gender (male, ref)	0.82 (0.70–0.96)	0.012	0.75 (0.61–0.91)	0.003	0.77 (0.66–0.91)	0.001
Age	1.00 (0.99–1.01)	0.822	1.00 (0.99–1.00)	0.225	0.99 (0.98–1.00)	0.024
Disease stage (stage III, ref)	1.32 (1.10–1.61)	0.005	1.32 (1.08–1.61)	0.006	1.32 (1.09–1.61)	0.005
PS 1 (PS 0, ref)	1.29 (1.06–1.57)	0.010	1.24 (1.02–1.52)	0.033	1.24 (1.02–1.51)	0.035
PS 2 (PS 0, ref)	2.11 (1.68–2.65)	<0.001	1.89 (1.49–2.40)	<0.001	1.89 (1.49–2.40)	<0.001
BMI	0.97 (0.96–0.99)	0.009	0.99 (0.97–1.01)	0.358	0.97 (0.95–0.99)	0.004
Loss of appetite, yes (ref no)	1.47 (1.26–1.72)	<0.001	1.34 (1.13–1.58)	0.001	1.32 (1.12–1.56)	0.001

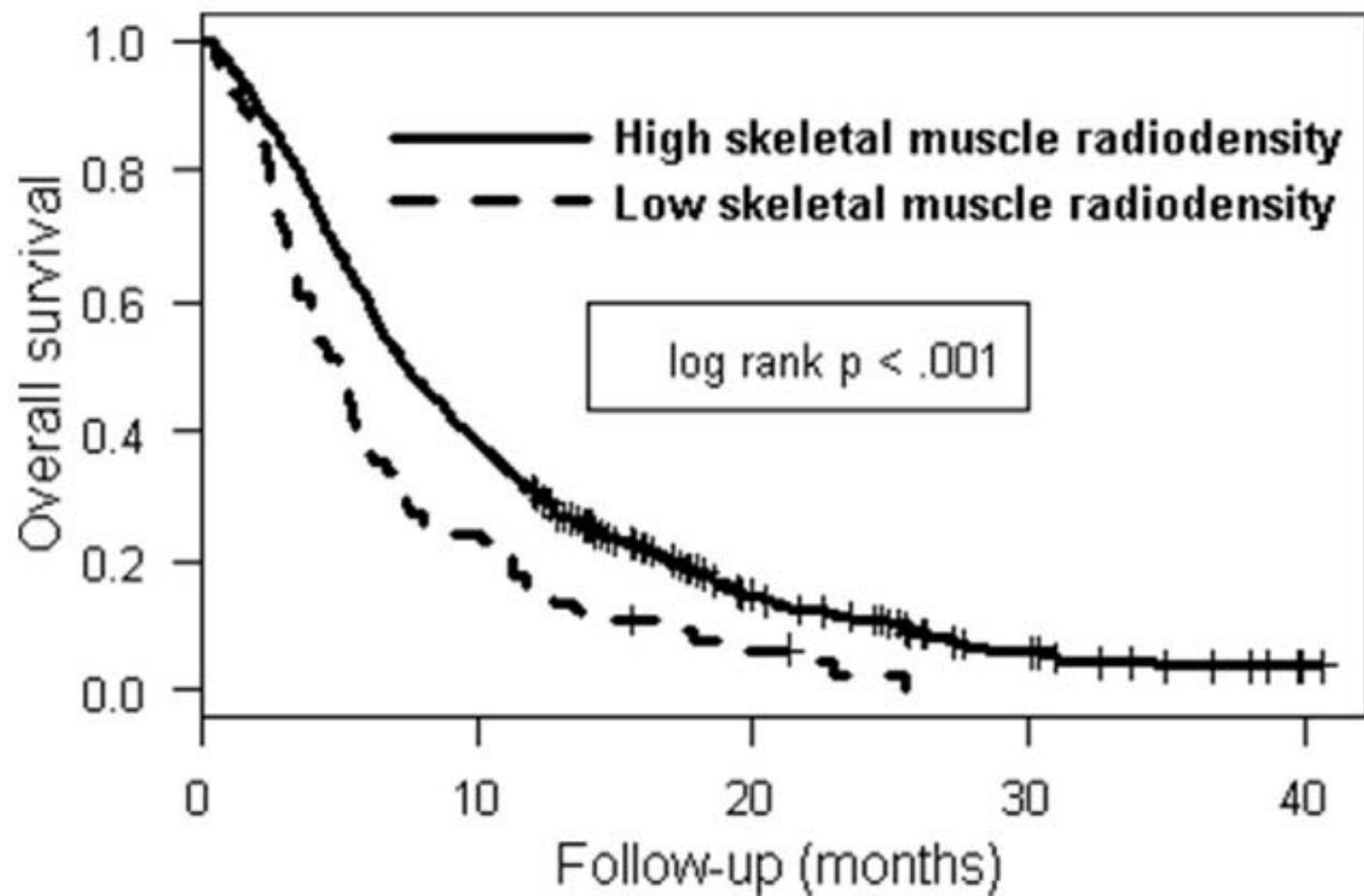
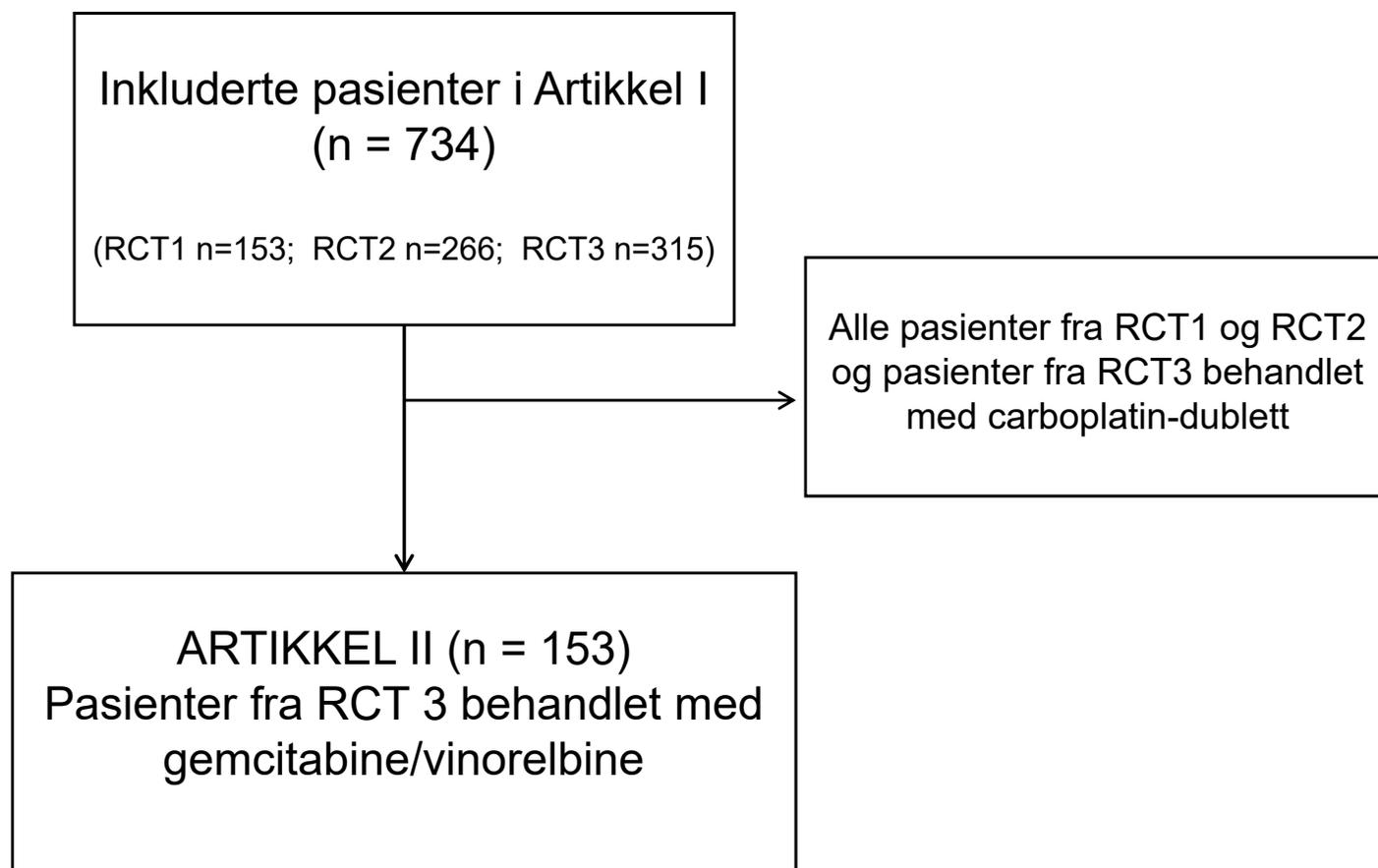


Fig. 2. Kaplan–Meier curves comparing overall survival between patients (both genders) with low versus high skeletal muscle radiodensity (SMD) (cut point 28.0 HU for men and 23.8 HU for women).



Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer

Björg Sjøblom^{a,b,*}, Bjørn H. Grønberg^{c,d}, Jūratė Šaltytė Benth^{e,f}, Vickie E. Baracos^g, Øystein Fløtten^h, Marianne J. Hjørnstad^{d,i}, Nina Aass^{i,j}, Marit Jordhøy^{a,j}



Primært endepunkt:

Hematologisk toksitet, CTCAE grad 3-4 etter syklus 1

Sekundært endepunkt:

Dosereduksjon $\geq 20\%$ (sammenlignet med startdose) og/eller seponering av behandling etter første syklus grunnet toksitet

Dose cytostatika per kilo LBM

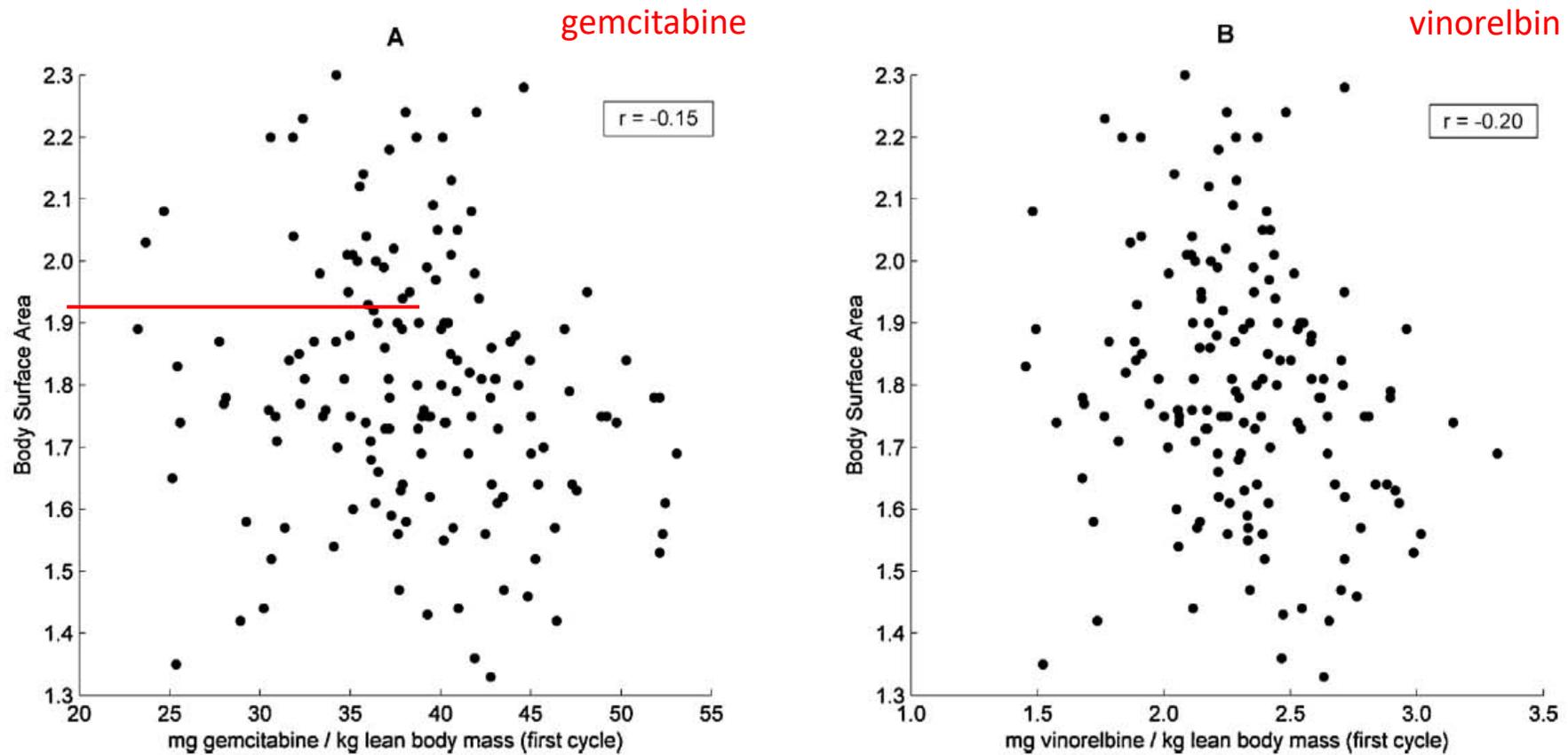
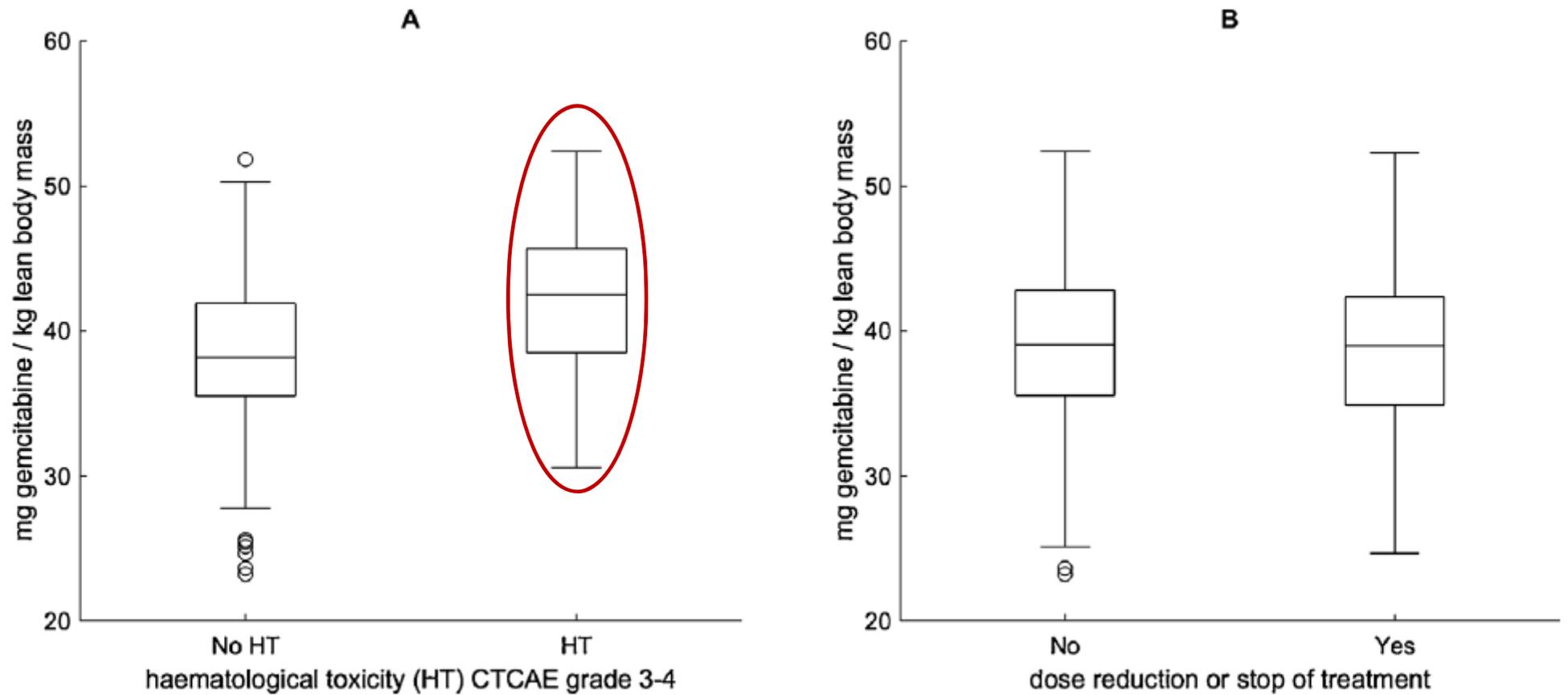


Fig. 2. Distribution of mg dose of gemcitabine (A) and vinorelbin (B) per kg lean body mass (LBM), in relation to body surface area.



Mean dose gemcitabine pr kg LBM var høyere hos de pasientene som hadde CTCAE grad 3-4 hematologisk toksisitet

Table 3
Regression analyses on toxicity.

	Haematological toxicity grade 3–4			
	Bivariate analyses		Multivariate analyses	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gemcitabine				
Gemcitabine (mg) / LBM (kg)	1.12 (1.03–1.23)	0.008	<u>1.15 (1.02–1.29)</u>	<u>0.018</u>
Age	0.96 (0.91–1.01)	0.126	0.96 (0.90–1.03)	0.262
Gender (male, ref)	2.21 (0.90–5.44)	0.084	0.86 (0.25–2.94)	0.812
Disease stage	2.38 (0.78–7.25)	0.126	3.02 (0.78–11.75)	0.111
Performance status	0.51 (0.14–1.86)	0.304	0.66 (0.16–2.70)	0.558
BMI	1.07 (0.97–1.18)	0.156	1.13 (1.01–1.26)	0.041
Loss of appetite	0.95 (0.39–2.31)	0.916	1.48 (0.52–4.23)	0.462
Vinorelbine				
Vinorelbine (mg) / LBM (kg)	7.08 (1.55–32.30)	0.011	<u>10.42 (1.36–80.0)</u>	<u>0.024</u>
Age	–	–	0.97 (0.90–1.03)	0.292
Gender (male, ref)	–	–	0.98 (0.31–3.16)	0.977
Disease stage	–	–	3.07 (0.80–11.78)	0.130
Performance status	–	–	0.68 (0.17–2.84)	0.600
BMI	–	–	1.13 (1.01–1.26)	0.039
Loss of appetite	–	–	1.30 (0.46–3.69)	0.617

Original Study



Drug Dose Per Kilogram Lean Body Mass Predicts Hematologic Toxicity From Carboplatin-Doublet Chemotherapy in Advanced Non-Small-Cell Lung Cancer

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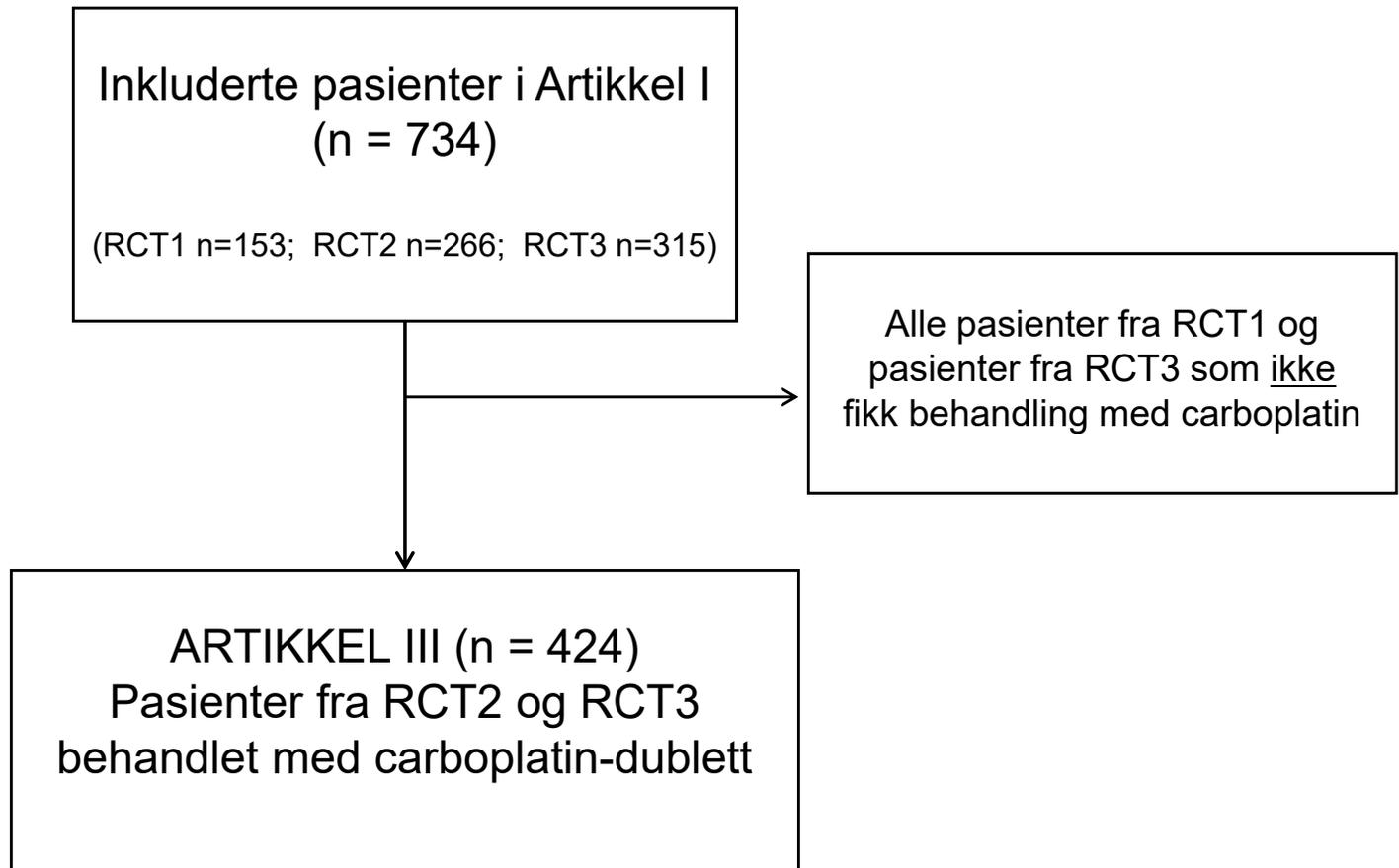
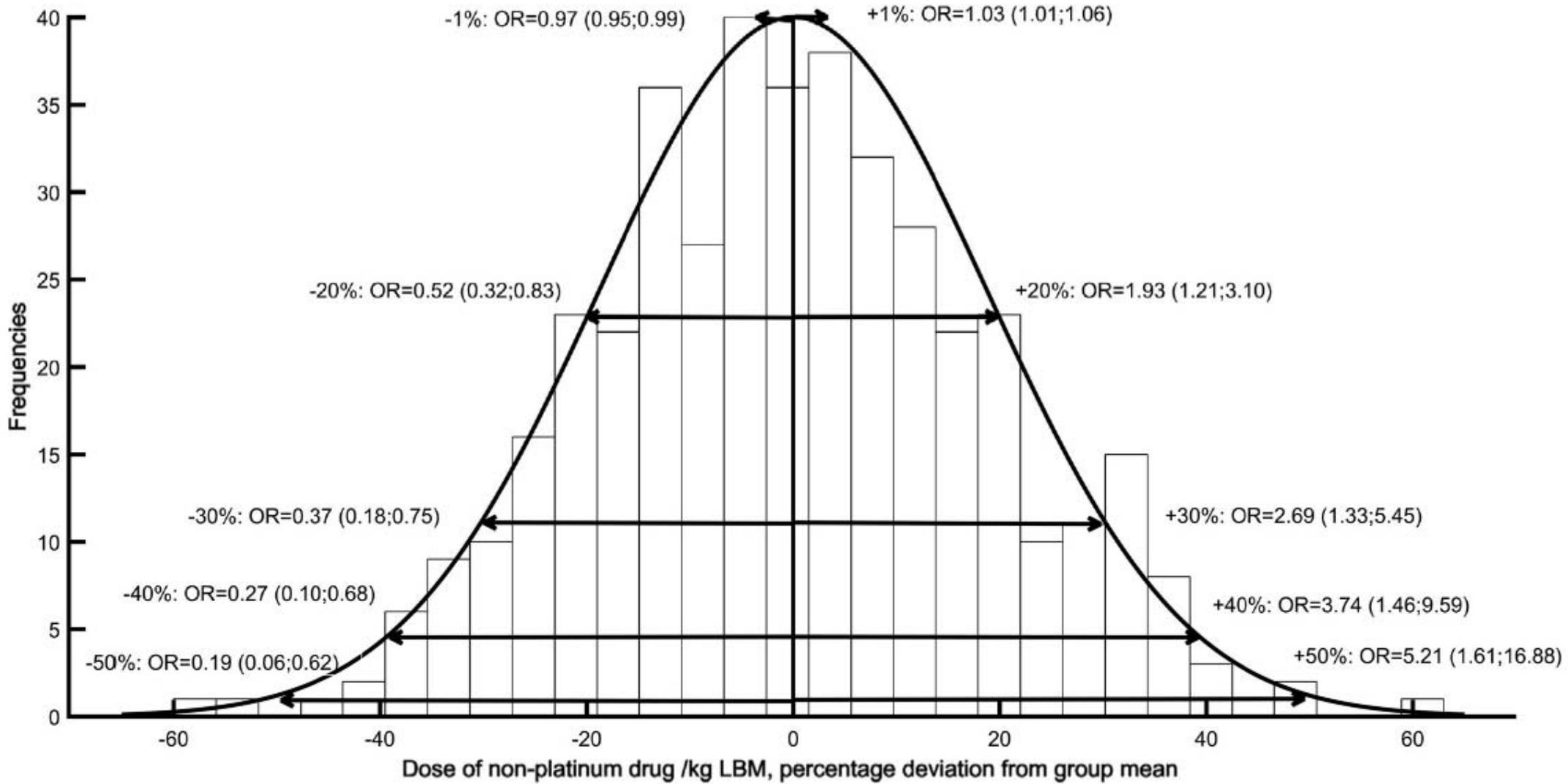


Table 3 Logistic Regression Analyses for Hematologic Toxicity CTCAE Grade 3/4^a

Covariate	Bivariate Model		Multivariate Model	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Drug Dose Per Kilogram of LBM				
Carboplatin ^b	1.01 (0.95-1.07)	.872	0.99 (0.88-1.11)	.865
Nonplatinum drug ^c	1.01 (1.00-1.03)	.050	1.03 (1.01-1.06)	.004
Treatment Subgroup				
GC	4.93 (2.68-9.09)	<.001	5.25 (2.77-9.95)	<.001
VC	0.75 (0.39-1.43)	.384	0.73 (0.37-1.43)	.357
PC (Ref.)	1		1	
Additional Covariates				
Age	1.03 (1.00-1.05)	.052	1.04 (1.01-1.08)	.024
Sex (male = Ref.)	0.78 (0.49-1.24)	.779	0.43 (0.23-0.83)	.011
BMI	1.00 (0.94-1.07)	.977	1.01 (0.94-1.09)	.765
Loss of appetite	1.28 (0.81-2.03)	.287	1.33 (0.78-2.27)	.304
Stage	1.05 (0.61-1.81)	.865	1.23 (0.65-2.31)	.532
Performance status ^d	1.30 (0.74-2.28)	.362	1.26 (0.66-2.43)	.484



Oppsummering

- Stor variasjon i kroppssammensetning
- Muskelmassens røntgentetthet var assosiert med overlevelse
- Mengden muskelmasse var ikke assosiert med redusert overlevelse
- Høyere dose av cellegiftstoffer per kg LBM av stoffer dosert ut fra BSA ga økt risiko for hematologisk toksisitet
- Kroppssammensetning kan ha betydning for toksisitet av cellegiftbehandling
- Kan man bedre individualisere dosering av cellegift ved å ta hensyn til kroppssammensetning?